time and the appropriate fee. The Examiner is requested to consider the remarks therein. Re-examination is respectfully requested.

AMENDMENTS

In the Claims:

Please amend the claims as follows:

1. (Amended) A composition comprising a first polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions and a neutral lipid associated with said first polynucleotide, and wherein said composition contains no cationic lipid.

2. (Amended) The composition of claim 1, wherein said first polynucleotide is an oligonucleotide having a length of between about 8 and about 50 bases.

3. (Amended) The composition of claim 1, wherein the first polynucleotide [hybridizes] is complementary to the translation initiation site of Bcl-2 mRNA.

6. (Amended) The composition of claim 5, wherein the first polynucleotide is encapsulated in the liposome.

9. (Amended) A composition comprising an expression construct that encodes a first polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular

conditions, wherein said first polynucleotide is under the control of a promoter that is active in eukaryotic cells, and wherein said construct is associated with a neutral lipid, and further wherein said composition contains no cationic lipid.

10. (Amended) A method of inhibiting proliferation of a Bcl-2-associated disease cell comprising obtaining a first polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions, mixing the first polynucleotide with a neutral lipid to form a composition comprising a polynucleotide/lipid association, and administering said association to [a] said Bcl-2-associated disease cell, wherein said cell expresses both Bcl-2 and Bax.

13. (Amended) The method of claim 10, wherein said first polynucleotide is an oligonucleotide having a length of between about 8 and about 50 bases.

15. (Amended) The method of claim 14, wherein the liposome encapsulates the first polynucleotide.

16. (Amended) The method of claim 10, wherein said [contacting] administering takes place in an animal.

RESPONSE TO OFFICE ACTION

I. Status of the Claims

Claims 1, 2, 3, 6, 9, 10, 13, 15, and 16 have been amended.

Claims 1-20 are presently in the case.

II. Rejection of Claims 10-20 Under 35 U.S.C. § 112, First Paragraph

The Action has first rejected Claims 10 - 20 as being unpatentable under 35 U.S.C. § 112, first paragraph, for failing to teach how to make and/or use the invention. The Action takes the position that the specification does not teach how to identify a bcl-2 associated disease cell that is treatable by the claimed antisense technology, and further that no bcl-2 disease has been shown to be treated by antisense and therefore the method is unpredictable.

This rejection is respectfully traversed. Applicants submit that on the contrary, the specification more than adequately describes how to make and use the claimed invention. The specification describes the use of liposomal antisense bcl-2 in cells that overexpress bcl-2. In Johnson cells used as a model in the present disclosure, overexpression is due to a t(14;18) translocation as described in the specification at page 34. At page 38, the specification again states that the inhibition of cell growth was seen in those cells with the t(14;18) translocation, and not in those cells that do not have the translocation and do not overexpress Bcl-2. In addition, the specification at page 37 describes the role of the Bcl-2/Bax ratio in the induction of apoptosis. Therefore the present specification does describe how to use the present invention, by choosing cell lines that overexpress Bcl-2 and that also express Bax.

Turning to the Action's objection regarding the unpredictability of antisense technology, Applicants assert that the specification is fully enabling for the claimed methods. Examiner's attention is drawn to the specification at page 5, the paragraph beginning on line 16, for a description of a method of treating a cancer cell, including treatment in a human. For example, the composition may be delivered to a human patient in a volume of 0.50-10.0 ml per dose or in an amount of 5-30 mg polynucleotide per m^2. The composition may also be delivered 3 times per week for 8 weeks. The following paragraphs describe how to select a polynucleotide for antisense therapy, the formation of liposomes as carriers of the polynucleotides and the use of an expression vector to express the polynucleotide.

In the specification at page 10, line 25, through page 13 is a section that further describes how one would design a complementary oligonucleotide, and how one would determine binding of the oligonucleotide in intracellular conditions to confirm antisense activity.

Therefore, the specification is fully enabling for how to make and use the claimed invention.

The Examiner also expresses concerns about whether the invention has *in vivo* utility based on the *in vitro* data provided in the specification. As stated in the M.P.E.P. §2107.02 (c.),

> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process.

As regards the Action's argument that no trial of antisense oligonucleotides in gene therapy has been successful, Applicants point to the last statement in (M.P.E.P. §2107.02 (c), "The mere fact that something has not previously been done clearly is not, in itself, a sufficient

basis for rejecting all applications purporting to disclose how to do it." It appears that the present rejection is in direct opposition to that statement, and that the rejection should be withdrawn.

The only concern of the Patent Office should be the truth of the statements in the specification. Applicants respectfully submit that 35 U.S.C. § 112, first paragraph requires only objective enablement. *The Office must show sufficient reason why one skilled in the art would not find the disclosure adequate to teach how to make and use the invention.* See for example, *In re Marzocchi and Horton*, 169 USPQ 369 (1971) wherein the court emphasized the need for the Patent Office to present reasons to doubt the "objective truth of the statements therein which must be relied on for objective support." No such statements are found in the Action.

In further evidence of the credibility of the statements in the present application, Applicants submit herewith as Exhibit "A" a declaration of Dr. Ana M. Tari and Dr. Gabriel Lopez-Berestein which describes *in vivo* studies that were done using the compositions and methods of the claimed invention. As shown in the declaration, the mouse studies conducted in the laboratory of the inventors demonstrates that the inventors observed definite morphological differences in tumor bearing mice treated with liposomal anti-Bcl-2 oligonucleotides compared to untreated or control treated mice. This data shows that their is a reasonable correlation between the described activity and the asserted utility. Therefore, the Patent Office is required to withdraw this rejection. Such favorable action is respectfully requested.

Applicants conclude that in light of the preceding discussion, the specification is enabling for the claimed subject matter and request withdrawal of this rejection.

III. Rejection of Claims 1-20 Under 35 U.S.C. § 112, Second Paragraph

The Action has rejected Claims 1-20 under 35 U.S.C. § 112, second paragraph, as being indefinite and for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

Claims 1-20 are rejected as vague and indefinite as drawn to a polynucleotide that hybridizes to a Bcl-2 encoding polynucleotide. Applicants have further clarified the subject matter of claims 1-20 by amending the claims to include the conditions under which a polynucleotide of the present invention will hybridize to a Bcl-2 encoding polynucleotide. Intracellular conditions are defined in the specification at page 11, the paragraph beginning on line 14.

Claims 2-4 have been amended to more clearly define to what "said polynucleotide" refers.

The subject matter of claim 9 has been further clarified by use of the term second polynucleotide as suggested by the Examiner. However, Applicants traverse the statement in the Action that the claim is vague and indefinite because it recites "only one product in the composition." Applicants submit that an expression construct is a composition of matter, and that the use of the term comprising leaves the claim open to the inclusion of unspecified ingredients. Such an open claim is neither vague nor indefinite.

Applicants have clarified the language of the pending claims to fully address the stated concerns under § 112, 2nd paragraph, and believe the claims now even more particularly point out and distinctly claim the subject matter that the Applicants regard as their invention. Applicants respectfully request, therefore, that these rejections be withdrawn.

IV. Rejection of Claims 1, 2, 5 and 6 Under 35 U.S.C. § 102(a)

The Action rejects claims 1 and 2 under 35 U.S.C. §102(a) over the abstract of Almazan *et al.* and claims 1, 2, 5 and 6 under 35 U.S.C. §102(a) over the abstract of Tormo *et al.*

Turning first to Almazan et al., Applicants traverse on the grounds that the Almazan abstract does not teach the subject matter of claims 1 and 2, and in addition, such a brief description of the work as appears in this abstract is not an enabling disclosure. However, in order to progress the present case towards allowance, Applicants choose to demonstrate herein that the Almazan and the Tormo references are not available as prior art to the present disclosure in that the claimed invention was conceived and reduced to practice in this country prior to March, 1996 and thus prior to the publication of the Almazan and Tormo abstracts.

In evidence that the invention was made and tested in this country prior to March, 1996, attached hereto as Exhibit "B" is a declaration of Dr. Gabriel Lopez-Berestein and Dr. Ana M. Tari. This declaration shows the present inventors had made the liposomal antisense Bcl-2 compositions and had tested the effect of those compositions, including growth inhibition and apoptotic index, on four lines of cells prior to the publication of the cited abstracts.

V. Rejection of Claims 1-6 and 9 Under 35 U.S.C. § 102(b) or § 102(e)

Claims 1-6 and 9 are rejected under 35 U.S.C. § 102(b) as being anticipated by Evan, or under 35 U.S.C. § 102(e) as anticipated by Green, and claims 1-6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Reed.

Applicants find no teaching in the cited references of a polynucleotide associated with a neutral lipid and no cationic lipid, as in the rejected claims. Therefore the claims are clearly distinguished from the cited references and the rejections under 35 U.S.C. § 102(b) and (e) are moot.

VI. Rejection of Claims 7 and 8 Under 35 U.S.C. § 103(a)

Claims 7 and 8 have been rejected under 35 U.S.C. § 103 as being unpatentable over Evan *et al.* or Reed *et al.* or Tormo *et al.* or Green *et al.* in view of Ledley.

In response, Applicants' submit that these references, either alone or in combination, can in no way be said to teach or suggest the subject matter of claims 7 and 8, in which a polynucleotide is associated with a phosphatidylcholine, a phosphatidylglycerol or a phosphatidylethanolamine. Applicants find no teaching in Ledley that such neutral phospholipids make highly efficient liposomes, as stated in the Action.

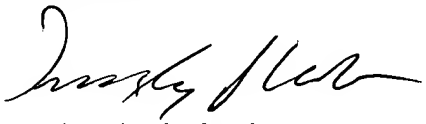
Rather, Ledley appears to state that formulations of DNA with DOTMA (a cationic lipid) combined with a neutral lipid or cholesterol facilitate highly efficient gene transfer. Applicants' reading of the cited passage in Ledley suggests that the cationic lipid is a necessary component of the DNA delivery formulation of Ledley, and thus teaches away from a formulation as in rejected claims 7 and 8 in which a polynucleotide is associated with a neutral lipid such as a phosphatidylcholine, a phosphatidylglycerol or a phosphatidylethanolamine in the absence of a cationic lipid.

Therefore, since Applicants find no teaching nor suggestion of the claimed invention in the cited references, Applicants respectfully request that this rejection be withdrawn.

VII. Conclusion

In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance and such favorable action is respectfully requested. If the Examiner has any questions or comments, or believes that certain amendments of the claims might more readily progress this case toward allowance, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,



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